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Letter to the Editor

Rare Case of De Novo Interstitial Deletion 2q13q21: Clinical, Cytogenetic, and Molecular Studies

To the Editor:

In humans, cytogenetically visible autosomal deletions have a live birth incidence of ~1 in 7,000 [Jacobs et al., 1992]. Interstitial deletions in the long arm of chromosome 2 appear to be rare. To the best of our knowledge, 28 different interstital deletions in the long arm of chromosome 2 have been described so far [for review: Boles et al., 1995; McMilin et al., 1998]. Among these cases is a wide diversity with respect to size and localisation of the deletion, leaving some regions of chromosome 2 underrepresented. Whereas deletions of the bands 2q24q31 have been reported several times, deletions in the region 2q14 have been described only five times [German et al., 1973; Antich et al., 1983; Lucas et al., 1987; Frydman et al., 1989; Davis et al., 1991]. In two of these, premature craniosynostosis was observed. Therefore, Brewer et al. [1998] proposed an association of this finding with del(2)(q14q21).

Here, we present the clinical, cytogenetic and molecular findings in a 6-year-old, mentally retarded boy who is a carrier of the rarely observed interstitial deletion 2q13q21. The child has a broad spectrum of craniofacial anomalies but no craniosynostosis. Further manifestations include delayed psychomotoric development and short stature.

CLINICAL REPORT

B.D. is the second child of healthy, distantly related Turkish parents, ages 22 (mother) and 26 (father) years. His older brother is healthy. After an uneventful pregnancy and spontaneous delivery at 37 weeks, birth weight was 3,410 g, length 51 cm, and head circumference 35 cm. Apgar scores were 8/9/9.

Multiple anomalies were noticed: large, dysplastic, low set ears, upsweep of anterior hairline, downslanting palpebral fissures, prominent mandible, widely spaced nipples, large distance between thumb and forefinger, bilateral postaxial hexadactyly (which was operated postpartum), syndactyly of toes, diastasis recti, and muscle hypotonia. The boy suffered from nasal breathing difficulties.

Microcephaly and growth retardation developed postnatally. At the age of 6 years, head circumference was 49.3 cm (< 3rd centile), body weight was 19.8 kg (25th centile), and stature was 104.1 cm tall (< 3rd centile).

Motor and mental development were delayed from the beginning. Unsupported sitting was achieved at 12 months and walking at 3 years. At this age, serum concentrations of IGF-I, IGF-II, and IGFBP3 were decreased (28 ng/ml, 391 ng/ml, 1600 ng/ml, respectively), suggesting growth hormone deficiency.

At 6 years, he was able to speak two-word sentences and to understand easy verbal expressions. His overall development is currently slow but steady.

CYTOGENETIC AND DNA STUDIES

GTG-banded lymphocyte chromosomes at the 400-band level consistently showed a small deletion in the long arm of chromosome 2, resulting in the following karyotype: 46,XY,del(2)(q13q21). Both these breakpoints correspond to fragile sites in 2q as described by Palmer et al. [1990]. Parental karyotypes were normal indicating that the deletion in the patient was de novo. A cell line of the patient is available.

The microsatellite D2S121, which is located in the deleted region, was typed by PCR and sequencing gel electrophoresis. For this marker, the patient had inherited only one maternal allele. Thus the deletion was of paternal origin (data not shown). Typing of further chromosome 2 markers (D2S311, D2S117, D2S116, D2S325, D2S118) outside the deletion indicated biparental inheritance of chromosomes 2.

DISCUSSION

It is a fundamental concept that patients with identical or overlapping chromosomal deletions share certain clinical findings. Thus autosomal deletions may be useful for human gene mapping [Ferguson-Smith and Aitken, 1982] in particular deletions that are not combined with a partial trisomy of an autosomal region.

If this assumption is correct, the association of segmental aneuploidy with a certain malformation may help to localize and subsequently clone the specific malformation-causing gene(s). An attempt to facilitate the search for such disease-associated genes has been

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TABLE I. Comparison of Clinical Data of Five Previously Described Cases With Deletions in 2q12-q21 and of the Present Case*

Clinical data	German et al., 1973 del(2)(q14)	Antich et al., 1983 del(2)(q12q14)	Lucas et al., 1987 del(2)(q14q21)	Frydman et al., 1989 del(2)(q13q21)	Davis et al., 1991 del(2)(q13q21)	Present case del(2)(q13q21)
Growth retardation	+	+	–	+	?	+
Psychomotor retardation	+	+	–	+	+	+
Hypotonia	?	?	+	?	+	+
Craniofacial anomalies	+	+	+	+	?	+
Premature craniosynostosis	+	?	+	?	?	–
Prominent forehead	?	+	+	?	?	+
Downslanting palpebral fissures	+	+	+	?	?	+
Cleft palate	?	+	–	–	–	–
Low set ears	?	+	+	+	?	+
Short neck	?	+	–	+	?	+
Syndactyly of toes	–	–	–	?	?	+
Cardiac malformations	?	+	–	+	+	–
Postaxial hexadactyly	–	of toes	–	?	?	of fingers
Agenesis of corpus callosum	?	?	?	+	+	–
Eye anomalies	?	?	?	+	?	–

*?, not ascertained.

undertaken by the construction of a systematic chromosomal deletion map in humans [Brewer et al., 1998].

To the best of our knowledge, the number of reported cases with deletions overlapping in 2q14 amounts to six (Table I) with this case. The patients share some phenotypically nonspecific common findings such as growth and mental retardation as well as some craniofacial anomalies. Nevertheless, the clinical picture is variable, possibly in relation to nonidentical breakpoints. When comparing the patients with del(2)(q14), two of them showed postaxial hexadactyly. Premature craniosynostosis was present as a main finding in two further patients (Table I). Brewer et al. [1998] therefore suggest that the latter malformation might be associated with deletion of the chromosomal region 2q13-q14. However, neither our patient, nor those described by Antich et al. [1983], Frydman [1989], and Davis [1991], show premature craniosynostosis.

The question remains whether growth retardation in our case is due to growth hormone deficiency or to the chromosomal rearrangement. The deletion in our case is of paternal origin as are most of structural aberrations. For the other deletions in 2q12-q2 1 the parental origin is not known. There might also be yet unknown parent-of-origin effects that could modify the clinical picture of autosomal deletions.

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